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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

BALLARD, KIMBERLY A

ART UNIT PAPER NUMBER

1649

DATE MAILED: 01/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/683,815	Applicant(s) ROSENTHAL ET AL.	
	Examiner Kimberly A. Ballard	Art Unit 1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 November 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-50 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-50 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) ☒ Notice of References Cited (PTO-892) | 4) ☐ Interview Summary (PTO-413) |
| 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) ☐ Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>8/30/04, 9/27/05</u> | 6) ☐ Other: _____ |

DETAILED ACTION

Status of Application, Amendments, and/or Claims

Claims 1-50 are pending and currently under examination in this office action.

The Examiner of U.S. Patent Application No. 10/683,815 has changed. In order to expedite the correlation of papers with the application, please direct all future correspondence to Examiner Ballard, Technology Center 1600, Art Unit 1649.

Claim Objections

Claims 8, 9, 20, 21, 33, 34, 46, and 47 are objected to because of the following informalities: According to the sequence listing submitted by Applicant on March 30, 2004, SEQ ID NO: 4 is a nucleic acid sequence, however, the claims recite "a monoclonal antibody comprising amino acid sequence of SEQ ID NO: 4 and 6." SEQ ID NO: 6 is the amino acid sequence encoded by the nucleic acid sequence of SEQ ID NO: 4. It appears that the sequence ID numbers for SEQ ID NO: 4 and 5 have been reversed in the CRF listing compared to the sequences listed on p. 74 of the specification. Appropriate correction is required.

Claims 1-50 are objected to because of the following informalities: the claims recite a "pharmaceutical acceptable carrier". A more grammatically correct phrase would recite "pharmaceutically acceptable carrier." Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of *reducing pathology* associated with Alzheimer's disease in transgenic mice, does not reasonably provide enablement for a method of *delaying development of* a symptom associated with Alzheimer's disease as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are broadly drawn to a method of delaying development of a symptom associated with Alzheimer's disease in a subject comprising administering a pharmaceutical composition comprising an antibody that binds preferentially to amino acids 28-40 of A β ₁₋₄₀ peptide. The Examiner thus interprets the claim to encompass prevention of Alzheimer's disease (AD) in any given individual, because, as the etiological cause has not yet been clearly defined for all cases of AD, any given individual is potentially susceptible to developing AD and therefore everyone would be eligible for the instant treatment method wherein the development of symptoms associated with Alzheimer's disease are delayed.

The specification discloses that treatment with various anti-A β monoclonal antibodies in transgenic mice over-expressing the 'Swedish' mutant amyloid precursor

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protein (APP; Tg2576 transgenic line) resulted in a substantial percentage (40-80%) decrease in both A β deposits and thioflavine-S deposits (the toxic fibrillar form of A β deposits). See for example, Example 5, p. 65-66. However, while the use of Tg2576 mice is an excellent model for studying Alzheimer's disease, it is not an appropriate model for studying the effects of preventative treatment with anti-A β antibodies in the general population. Tg2576 transgenic mice over-express human amyloid precursor protein (APP) and have been shown to develop much of the pathology associated with Alzheimer's disease (see, for example, Hsiao et al. *Science*, 1996, 274: 99-102, as cited on Applicant's IDS received 8/30/04). As the age of the mice increases, so do both behavioral deficits and brain levels of A β increase (see Hsiao, Figure 2, p. 100, and Table 1, p. 102). Wild-type or out-bred mice, which would more closely model a general human population in regards to susceptibility to Alzheimer's disease, do not present such pathology. Therefore, the effect of anti-A β antibody therapy in non-transgenic mice, which have low levels of central A β in comparison to Tg2576 mice, would presumably be different, both qualitatively and quantitatively, than what is observed in Tg2576 transgenic animals, which have elevated central A β levels. There is no disclosure of preventative treatment of non-transgenic (wild-type) animals for neurological pathology using anti-A β antibodies. Thus, the model system used in the instant specification is not recognized as providing for teachings that are predictive of the results that would be expected for the full scope of the claims. For example, the art recognizes that such *in vivo* models are not readily correlated to the human *in vivo* case. In particular, the art teaches a lack of correlation of beneficial effects shown in

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the mouse model system in humans; see in particular Münch & Robinson (July 2002, "Potential Neurotoxic Inflammatory Responses to A β Vaccination in Humans." *J. Neural Transmission*, 109(7-8): 1081-1087).

Also, a delay in the development of symptoms, or prevention, is understood in the art to mean a total protection from disease or injury. Thus, given the high level of required effect, a high level of evidence showing prevention is also required. While the specification demonstrates a level of protection using anti-A β antibodies for passive immunization in the Tg2576 mice, total prevention was not achieved.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

Regarding the nature of the invention, both at the time of filing and now, effective therapy for the prevention of Alzheimer's has eluded researchers. De Lustig et al. (*Rev in Neurosciences*, 1994, 5: 213-225) report that there is still no adequate preventive strategy and no effective therapies for the pathology, and the disease thus follows an inevitable degenerative course. And in a recent review by Vickers (*Drugs Aging*, 2002, 19(7): 487-494), it is noted that there is no effective treatment currently available to reverse, slow down or prevent the course of Alzheimer's disease and most other brain diseases and conditions.

On the state of the prior art, Walker et al. (July 1994, "Labeling of Cerebral Amyloid In Vivo with a Monoclonal Antibody." *J Neuropath Exp Neurology*, 53(4): 377-383, recited on Applicant's IDS received 9/27/05) teach the administration of a monoclonal anti- β -amyloid antibody (10D5) into the cerebrospinal fluid of aged monkeys (p. 377). Following injection, the monkeys were sacrificed and their brains examined to confirm that the injected antibodies had labeled A β plaques (Figures 1-5). It is noted that the monoclonal anti- β -amyloid antibody (10D5) did not disaggregate, prevent, or inhibit A β aggregation.

Due to the large quantity of experimentation necessary to determine the effectiveness of preventative treatment in subjects, the lack of direction/guidance presented in the specification regarding the same, the complex nature of the invention, the state of the prior art with respect to such treatment, the unpredictability of preventative therapy as evidenced in the art, and the breath of the claims which effectively fail to limit a specific patient population, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

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1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 6, 10-16, 18, 22-24, 26-29, 31, 35-37, 39-42, 44, and 48-50 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4, 7-17, 19, 28, 31-40, and 42 of copending Application No. 11/194,989. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '989 application contains claims drawn to a method for treating a disease characterized by aberrant deposition of a protein in the brain of a subject, wherein the disease is Alzheimer's disease, comprising administering an antibody that specifically binds to the protein or an aggregated form of the protein, wherein the protein is β -amyloid peptide. Noted claim limitations of the '989 application corresponding to instant limitations include: a monoclonal antibody (claims 8 and 32), a humanized antibody (claims 9 and 33), a human antibody (claims 10 and 34), the antibody binds to $A\beta$ peptide with a K_D of about 100, 20, or 2 nM or less (claims 11-13, 35-37), the antibody binds to the C-terminus of $A\beta$ (claims 14, 16, and 39), the antibody specifically binds to an epitope within residues 28-40 of $A\beta_{1-40}$ (claims 15 and 38), the epitope includes amino acid 39 and/or 40 (claims 17 and 40), and the antibody binds to $A\beta_{1-40}$ with higher affinity than to $A\beta_{1-42}$ or $A\beta_{1-43}$ (claims 19 and 42). The $A\beta$

antibody binding affinity to A β of the '989 application is a species which would render obvious instant recitation of anti-A β -amyloid antibody Fab fragment affinity of 200 nM or less (instant claims 4, 6, 16, 18, 29, 31, 42, and 44). Thus, the '989 application claims render obvious the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-4, 6, 10-16, 18, 22-24, 26-29, 31, 35-37, 39-42, 44, and 48-50 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 6-15, 17, 26, 29-38, and 40 of copending Application No. 11/195,207. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '207 application contains claims drawn to a method for treating a disease characterized by aberrant deposition of a protein in the brain of a subject, wherein the disease is Alzheimer's disease (claims 3 and 29), comprising administering an antibody that specifically binds to the protein or an aggregated form of the protein, wherein the protein is β -amyloid peptide. Noted claim limitations of the '207 application corresponding to instant limitations include: a monoclonal antibody (claims 6 and 30), a humanized antibody (claims 7 and 31), a human antibody (claims 8 and 32), the antibody binds to A β peptide with a K_D of about 100, 20, or 2 nM or less (claims 9-11, 33-35), the antibody binds to the C-terminus of A β_{1-40} (claims 12, 14, and 37), the antibody specifically binds to an epitope within residues 28-40 of A β_{1-40} (claims 13 and 36), the epitope includes amino acid 39 and/or

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40 (claims 15 and 38), and the antibody binds to A β ₁₋₄₀ with higher affinity than to A β ₁₋₄₂ or A β ₁₋₄₃ (claims 17 and 40). The A β antibody binding affinity to A β of the '207 application is a species which would render obvious instant recitation of anti-A β -amyloid antibody Fab fragment affinity of 200 nM or less (instant claims 4, 6, 16, 18, 29, 31, 42, and 44). Thus, the '207 application claims render obvious the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 2, 4, 6, 8-10, 13, 14, 16, 18, 20-22, 25-27, 29, 31, 33-35, 38-40, 42, 44, and 46-48 are rejected under 35 U.S.C. 102(b) as being anticipated by Bard et al. (*Nat Med*, August 2000, 6(8): 916-919, cited on Applicant's IDS received 8/30/04).

The claims are drawn to methods of treating Alzheimer's disease, suppressing formation of amyloid plaques, reducing amyloid plaques, and delaying development of a symptom associated with Alzheimer's disease each comprising administering to the

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subject an effective amount of an antibody that preferentially binds to amino acids 28-40 of A β ₁₋₄₀ and a pharmaceutically acceptable carrier, with claim limitations reciting the antibody binding preferentially to an epitope that includes amino acid 39 and/or 40 of the A β ₁₋₄₀ peptide, the Fab fragment of the antibody having an affinity of about 200 nM or less, the antibody competitively inhibiting binding of a monoclonal antibody to A β ₁₋₄₀, the antibody is a monoclonal antibody, and the amyloid plaques are in the brain of the subject.

Bard et al. teaches the use of peripherally administered anti-A β antibodies to reduce pathology in PDAPP transgenic mice, a mouse model of Alzheimer's disease. Specifically, Bard et al. teach the administration of several different antibodies, both polyclonal and monoclonal, to decrease amyloid burden in the brains of the mice, thus meeting several instant claim limitations. Control animals were intraperitoneally injected with the vehicle PBS (phosphate buffered saline) (see p. 916, 1st column), which would have been used to dilute the antibodies for injection and thus meets the limitation of a pharmaceutically acceptable carrier. The monoclonal antibody 21F12 was employed in these studies (see p. 916-917), and is reported by this group to bind to A β ₃₃₋₄₂ (see, for example, US Patent No. 6,787,523 B1 to Schenk, September 7, 2004, filed November 30, 1998, column 34, Table 6). The 21F12 monoclonal antibody taught by Bard et al. would therefore meet the limitation of *preferentially* binding to amino acids 28-40 of A β ₁₋₄₀ as the epitope for 21F12 comprises A β ₃₃₋₄₀. The 21F12 monoclonal antibody would also therefore preferentially bind to an epitope that includes amino acid 39 and/or 40 of A β ₁₋₄₀ because these residues are also encompassed within the 21F12 epitope, thus

meeting a limitation of instant claims 2, 14, 27, and 40. It would be an expected property of the 21F12 monoclonal antibody to compete for binding with other antibodies, such as other monoclonal antibodies, which share the same epitope on A β ₁₋₄₀. Thus, the 21F12 would also competitively inhibit binding of a monoclonal antibody sharing the same epitope on the A β ₁₋₄₀ peptide, thus anticipating instant claims 8, 9, 20, 21, 33, 34, 46, and 47.

Bard et al. further teaches that the affinity for soluble A β (A β ₁₋₄₀ is the soluble form of A β) by 21F12 is 80 nM (see Table 1, p. 918) which would meet the instant claim limitation reciting the Fab fragment of the antibody, which is the antigen binding region, having an affinity of about 200 nM or less, thus anticipating instant claims 4, 6, 16, 18, 29, 31, 42, and 44. Bard et al. therefore anticipates the instant invention.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 2, 8-14, 20-27, 33-40, and 46-50 rejected under 35 U.S.C. 102(e) as being anticipated by US Patent No. 6,787,523 B1 to Schenk, September 7, 2004, filed November 30, 1998.

The claims are drawn to methods of treating Alzheimer's disease, suppressing formation of amyloid plaques, reducing amyloid plaques, and delaying development of a symptom associated with Alzheimer's disease each comprising administering to the subject an effective amount of an antibody that preferentially binds to amino acids 28-40 of A β ₁₋₄₀ and a pharmaceutically acceptable carrier, with claim limitations reciting the antibody binding preferentially to an epitope that includes amino acid 39 and/or 40 of the A β ₁₋₄₀ peptide, the antibody competitively inhibiting binding of a monoclonal antibody to A β ₁₋₄₀, the antibody is a monoclonal antibody, the antibody is a humanized antibody, the antibody is a human antibody, and the amyloid plaques are in the brain of the subject.

Schenk discloses methods of preventing or treating a disease characterized by amyloid deposition in a patient, wherein the amyloid deposit is aggregated A β peptide and the disease is Alzheimer's disease (column 2, lines 12-27). Schenk teaches the therapeutic use of an anti-A β antibody in the prevention or treatment of Alzheimer's disease (column 3, lines 37-42). Such antibodies can be monoclonal, humanized, or human antibodies to A β (column 10, line 62 – column 11, line 37) thus meeting specifically recited limitations of the instant claims. The agents (e.g. antibodies) are taught as being administered as pharmaceutical compositions comprising the active therapeutic agent (e.g. the antibody) and a pharmaceutically acceptable component such as non-toxic carriers or diluents, which are defined as vehicles commonly used to formulate pharmaceutical compositions for animal or human administration (column 16, lines 44-65). In therapeutic applications, compositions are administered to a patient in

an amount sufficient to cure, or at least partially arrest, the symptoms of the disease and its complications (i.e., a therapeutically-effective dose; column 14, lines 14-25).

Schenk further teaches the passive immunization of PDAPP mice with an anti-A β monoclonal antibody 21F12, which binds to the epitope A β ₃₃₋₄₂. Schenk teaches that the mice are injected as needed over a 4 month period to maintain circulating antibody concentration, at the end of which treatment the mice are euthanized and evaluated histologically for A β levels. PDAPP transgenic mice over-express human amyloid precursor protein (APP) and have been shown to develop much of the pathology associated with Alzheimer's disease, such as excessive A β deposits in the cortex and hippocampus (see, for example, Johnson-Wood et al. *PNAS*, February 1997, 94: 1550-1555). As Alzheimer's disease is characterized by the abnormal deposition of amyloid plaques in the brain (see Background, for example), it is understood that treatment of Alzheimer's disease encompasses any treatment that would affect the formation, accumulation/deposition, and/or overall amyloid burden in the brain, thus encompassing the methods of the instant claims.

The 21F12 monoclonal antibody taught by Schenk would meet the limitation of *preferentially* binding to amino acids 28-40 of A β ₁₋₄₀ as the epitope for 21F12, A β ₃₃₋₄₂, comprises A β ₃₃₋₄₀. The 21F12 monoclonal antibody would also therefore preferentially bind to an epitope that includes amino acid 39 and/or 40 of A β ₁₋₄₀ because these residues are also encompassed within the 21F12 epitope, thus meeting a limitation of instant claims 2, 14, 27, and 40. It would be an expected property of the 21F12 monoclonal antibody to compete for binding with other antibodies, such as other

monoclonal antibodies, which share the same epitope on A β ₁₋₄₀. Thus, the 21F12 would also competitively inhibit binding of a monoclonal antibody sharing the same epitope on the A β ₁₋₄₀ peptide, thus meeting limitations of instant claims 8, 9, 20, 21, 33, 34, 46, and 47. Thus, Schenk anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-14, 16-27, 29-40, and 42-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bard et al. (*Nat Med*, August 2000, 6(8): 916-919, cited on Applicant's IDS received 8/30/04) in view of Zeitlin et al. ("Preventing infectious disease with passive immunization." *Microbes and Infection*, 2000, 2: 701-708).

The claims are drawn to methods of treating Alzheimer's disease, suppressing formation of amyloid plaques, reducing amyloid plaques, and delaying development of a symptom associated with Alzheimer's disease each comprising administering to the subject an effective amount of an antibody that preferentially binds to amino acids 28-40 of A β ₁₋₄₀ and a pharmaceutically acceptable carrier, with claim limitations reciting the antibody binding preferentially to an epitope that includes amino acid 39 and/or 40 of the A β ₁₋₄₀ peptide, the Fab fragment of the antibody binds to A β ₁₋₄₀ with an affinity of 200 nM or 1 nM or less, the antibody competitively inhibiting binding of a monoclonal antibody to A β ₁₋₄₀ and having the same epitope to which said monoclonal antibody binds, the antibody is a monoclonal antibody, the antibody is a humanized antibody, the antibody is a human antibody, and the amyloid plaques are in the brain of the subject.

Bard et al. teaches the use of peripherally administered anti-A β antibodies to reduce pathology in PDAPP transgenic mice as set forth *supra*. Bard, however, does not teach lower antibody affinities for this monoclonal antibody (such as 1 nM or less) or humanized or human antibodies.

Zeitlin et al. teach that because of their high specificity and high affinity (typically 10^{-8} - 10^{-10} M) compared to polyclonal antibodies, monoclonal antibodies are currently used for treatment and prevention of specific diseases (see, for example, pp. 701-702). Zeitlin notes that an important benefit of the high potency that can be achieved with monoclonal antibodies is a marked increase in duration of protection, particularly when compared to other drugs such as antibiotics (see section 1.2, p. 702). Zeitlin speculates that if the affinity of the antibody were improved, the protective duration could also

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increase (p. 703, 1st column). Zeitlin teaches that monoclonals can be selected for defined activity against a specific epitope. Zeitlin further notes that with the advent of technology enabling the production of humanized or fully human monoclonals, immunogenicity problems are effectively reduced or eliminated, thus allowing monoclonal antibodies to achieve their full potential as clinically useful molecules (see section 2.3, p. 705).

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to arrive at the claimed invention by combining the methods of reducing amyloid burden in a Alzheimer's disease model using the monoclonal antibody 21F12 as taught by Bard et al. with selecting for a high affinity monoclonal and humanized or human monoclonals as taught by Zeitlin et al. to create high affinity anti-A β antibodies or humanized or human anti-A β antibodies for the treatment of Alzheimer's disease. The person of ordinary skill in the art would have been motivated to make these modifications because of the fact that an antibody with a higher affinity would be more specific to the disease being treated and could potentially extend the protective duration of the therapy as taught by Zeitlin et al. Further, the person of ordinary skill would have been motivated by immunogenicity problems encountered with murine monoclonal antibodies used therapeutically in humans to produce humanized or human monoclonal antibodies, which are much less likely than xenogenic antibodies to induce an immune response (such as an allergic response), as taught by Zeitlin (p. 705). One of skill in the art would have an expectation of success in treating Alzheimer's disease with an anti-A β antibody because Bard et al. teach that it

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would be expected to work (entire document). Accordingly, claims 1, 2, 4-14, 16-27, 29-40, and 42-50 are rejected under 35 U.S.C. 103(a).

Conclusion

Claims 1-50 are rejected.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kimberly Ballard, PhD
Art Unit 1649
January 13, 2006


JANET L. ANDRES
SUPERVISORY PATENT EXAMINER